REMARKS

Status Summary

An advisory action dated October 20, 2004, stated that the amendment filed on September 27, 2004, will entered for the purposes of appeal. A notice of appeal was filed on January 26, 2004. Claims 56-60 and 62-67 are pending. Claims 56-60 and 62-67 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Claims 56-60 and 62-67 are also rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson).

New claims 68-74 are added. Reconsideration in view of the new claims and following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 56-60 and 62-67 remain rejected and new claims 61-67 are also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Advisory action, page 2. This rejection is respectfully traversed.

Anderson describes methods for treatment of B cell lymphoma via administration of anti-CD20 antibodies. The examiner notes that Anderson does not teach treatment of CNS lymphomas, as now claimed. The examiner concludes that it would have been *prima facie* obvious to modify the methods of Anderson to "include B-cell lymphomas of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas." First official action (paper no. 7), pages 10-12.

The examiner relies on Caligiuri as teaching that primary CNS lymphomas involve the meninges, and on DeAngelis as teaching that lymphomas are a common cause of leptomeningeal metastases. Based thereon, the examiner concludes that one of ordinary skill in the art would reasonably expect that a subpopulation of patients with CNS lymphoma would also exhibit leptomeningeal lymphoma. Official action, pages 3-5. The examiner also

relies on Caligiuri and DeAngelis as teaching combination of immunotherapy with chemotherapy, as in claims 4, 53, and 58. Official action, pages 4-5, bridging paragraph.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicant responds that the examiner has failed to meet this burden given the lack of a reasonable chance of success in practicing the claimed invention.

Applicant has previously argued that, at the time of filing the instant application, a skilled artisan would not have had a reasonable chance of success in practicing the claimed invention based on unpredictability in treatments for CNS lymphomas. Specifically, the Caligiuri reference, which describes administration of anti-human Fas monoclonal antibodies, does not enable administration of anti-CD20 antibodies as now claimed.

In response to the foregoing argument, the examiner states that "[t]his argument has been considered but is not really well understood" and that "it's not clear how this argument is relevant to the current rejection." Advisory action, page 3, lines 3-5.

Applicant reiterates that the burden is on the examiner to establish a *prima facie* case of obviousness, which includes a showing that the claimed invention could be performed with a reasonable expectation of success. *See* MPEP § 2143. Where the cited documents do not expressly suggest the claimed invention, a showing of motivation also relies on a reasonable expectation of success. *See In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Therefore, the viewpoint of a skilled artisan with respect to expectation of success is essential to the establishment of a *prima facie* case of obviousness. Likewise, where such viewpoint does not include a reasonable expectation of success, as in the instant case, the claimed invention is non-obviousness.

The examiner further states that "[w]hile the Caliguiri reference does not specifically teach administration of the claimed anti-CD20 antibodies, one of ordinary skill in the art who reads the Caliguiri reference would understand that the primary lymphomas of the CNS are treatable with antibodies – a lesson which is particularly relevant to the teachings of the

Anderson patent which also concludes that lymphomas (in general) can be treated with antibodies." Advisory action, page 3, lines 16-20 (emphasis in original). Applicant responds that this conclusion constitutes the examiner's opinion only and is not supported by current evidence that treatment of CNS lymphomas and other CNS disorders remains highly unpredictable due to vulnerability of brain tissue to toxic leukoencephalopathy.

Cancer chemotherapeutics are familiar agents of toxic leukoencephalopathy, *i.e.*, damage to white matter following drug exposure. Based on the significant risks of toxic leukoencephalopathy, which may manifest as irreversible dementia and even death, only a small subset of chemotherapy and antineoplastic agents are administered intrathecally. For leukemia and lymphoma, intrathecal use is restricted to methotrexate (MTX), cytosine arabinoside (Ara-C) and corticosteroids. *See* Ruggiero et al. (2001) *Paediatr Drugs* 3(4): 237-246 (abstract enclosed). It is further recognized in the art that intrathecal administration of cancer drugs intended for systemic use only is dangerous and may result in a fatal outcome. *See* Ruggerio, 2001. For example, intrathecal administration of vincristine, a chemotherapeutic drug with proven efficacy following intravenous administration, resulted in the deaths of two patients within days following drug administration. *See* Dettmeyer et al. (2001) *Forensic Sci. Int.* 122(1): 60-64 (abstract enclosed). Even for the above-noted drugs that are used for direct CNS administration, toxic leukoencephalopathy may be fatal. *See e.g.*, Hara et al. (2000) *Breast Cancer* 7(3): 247-251 (abstract enclosed). In addition to concerns regarding toxicity, antibodies are also subject to metabolic elimination from the intrathecal space, which would defeat achievement of therapeutic levels of antibody. *See e.g.*, Blaney et al. (2000) *Med Oncol* 17:151-162, pages 156-7, bridging paragraph (copy previously submitted).

Based on the foregoing, drug efficacy observed following systemic administration cannot be extrapolated to efficacy of direct administration to the CNS. The risk of toxic leukencephalopathy following high dose or direct brain administration of cancer chemotherapeutics precludes a reasonable chance of success in performing, and in fact teaches away from, the claimed invention. Thus, contrary to the suggestion of the examiner, one skilled in the art would not be motivated to replace the anti-Fas antibody in the methods of Caliguiri with an anti-CD20 antibody of Anderson to arrive at the presently claimed invention.

In the absence of a motivation to practice the claimed invention based on a reasonable chance of success, the claims are not *prima facie* obvious. Accordingly, applicant respectfully requests that the rejection of claims 56-60 and 62-67 under 35 U.S.C. § 103(a) based on Anderson, Caligiuri, and DeAngelis be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 56-60 and 62-67 remain rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson). Advisory action, page 5. This rejection is respectfully traversed.

Based on the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Discussion of New Claims

New claims 68-74 are added. Claims 68 and 71 are directed to therapeutic methods that employ an anti-CD20 antibody conjugated to a toxin, drug, or enzyme. Claims 69-70 and 72-74 are directed to therapeutic methods that employ a radiolabeled anti-CD20 antibody. Support for new claims 68-74 can be found in the originally filed specification, including at page 37, line 30, through page 40, line 23, and at page 10, lines 9-14. *See also* original claims 20 and 39-42

U.S. Patent Appl. No. 09/840,872
Attorney Docket No. 037003-0280609

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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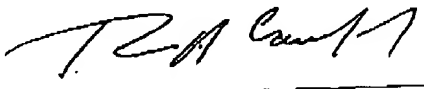

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